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14. ABSTRACT

Androgens are critical for the maintenance of brain structure and function with particular importance for maintaining memory. Thus, men on androgen deprivation therapy (ADT) are at risk for memory failure and decreased quality of life. Direct assessment of ADT effects on the brain have not been made but are now possible with modern noninvasive neuroimaging techniques and analysis tools. We used magnetic resonance diffusion tensor imaging to assess white matter integrity and functional magnetic resonance imaging (fMRI) to investigate ADT effects on the brain. Preliminary analyses suggest that men on ADT have more white matter loss in prefrontal cortex and poorer memory than expected for men in this age range. Men with prostate cancer have more prefrontal fMRI activity than healthy men. Additional analyses will examine group differences in specific regions of interest and relate brain activity to levels of memory performance. This study suggests that noninvasive imaging techniques will be useful to understand the long-term consequences of ADT.

15. SUBJECT TERMS
Prostate cancer; neuroimaging; neurocognition

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Introduction:

Androgen deprivation therapy (ADT) is the standard treatment for advanced prostate cancer and improves survival in patients with clinically localized, but high-risk prostate cancer (1;2). ADT is often used for prolonged periods of time in elderly men whose life expectancy exceeds 10-20 years. Neurocognitive toxicity is increasingly recognized (3) including memory loss and cognitive slowing, although these have not been well characterized and there is virtually no information on the neural basis of these complaints**. The goal of the study was to establish and test noninvasive neuroimaging methods to investigate the brain basis of cognitive decline in men on ADT.**

Studies using animal models show that testosterone modifies the physiology and function of memory regions of the brain. For instance, androgen deprivation causes a 40% decrease in synaptic density in the hippocampus of both rats (4) and monkeys (5). Lower testosterone levels are a premorbid risk factor for dementia (6) and beta amyloid levels, a risk factor for Alzheimer's disease, are higher in both animal models (7) and humans (8) after testosterone deprivation. We reported that men with prostate cancer on androgen deprivation therapy had impairments in verbal memory. In addition, we showed that the deficit was in the consolidation phase of memory (9;10).. The brain basis of the memory failure is unknown but fMRI that measures the blood oxygenation level dependent changes in neural activity induced by performance of a mnemonic task, and diffusion tensor imaging (DTI) that assesses the integrity of myelin and the membrane integrity of white matter tracts(11;12) are techniques that permit the assessment of ADT effects on the brain.

Body:

We present here the results of Aim 3 which demonstrate the techniques developed in Aims 1 and 2. To test these neuroimaging techniques, 11 men with prostate cancer (PC) on ADT, 12 men with PC who were not on ADT, and 12 healthy men without PC, were tested for verbal memory while we simultaneously obtained fMRI and DTI data. The men were recruited through OHSU's prostate cancer and urology clinics. The groups were matched for age, education and general verbal intellectual ability (See Table 1 in appendices). Two men were excluded from the fMRI analyses, and one from the DTI analyses due to technical errors. Men were excluded who had significant medical problems, clinical depression as assessed by the Geriatric Depression Scale or dementia as assessed by the Mini-Mental Status Exam or internal metal that would exclude them from MRI.

Cognitive activation during fMRI utilized a verbal memory measure (word lists) similar to the paradigm of (13). Subjects made judgments about whether word was a man-made or natural object as the encoding condition. This was interspersed with a control condition in which the subject made judgments about the direction of an arrow. Memory degradation was assessed by recognition tests at two (immediate and ~20 minute) retention intervals.

Image analysis for DTI was with FSL (http://www.fmrib.ox.ac.uk/fsl/) and Freesurfer (http://surfer.nmr.mgh.harvard.edu/) and we compared two regions of interest; the genu of the corpus callosum and white matter in prefrontal cortex. Brain Voyager fttp://www.brainvoyager.de) was used for fMRI analysis and both whole brain and two prefrontal regions of interest were examined.

Results: Memory degraded over the retention interval (immediate to delayed recognition) for all groups ($p < .01$). Men with ADT had poorer memory for words at both the immediate and delayed retention intervals ($p=.03$; See Fig. 1 in appendices). This is despite no difference between men with ADT and healthy men in speed or accuracy during encoding for the word or arrow task. Men with PC but who were not on ADT had performance that was intermediate between those on ADT and healthy men and did not differ from either. There was no group by retention interval interaction, suggesting that after initial encoding, memory decays at a similar rate in all groups.

During memory encoding, men with PC (both on ADT, Fig. 2b, and not on ADT, Fig. 2c) had amplified brain activity in prefrontal regions as compared to healthy men (Fig. 2a). We are currently doing region of interest analyses to compare prefrontal and medial temporal lobe regions to better define these differences. The source of the higher prefrontal activity in PC men and whether the activity is identical between men on ADT

and those not on ADT is currently under analysis. However, this suggests that men with PC utilize more prefrontal cortex to encode information than healthy men.

Men with ADT have less prefrontal white matter integrity than healthy men (See Fig. 3a). PC men not on ADT have white matter integrity between that of healthy men and men on ADT and do not differ from either group. This effect is specific to prefrontal white matter as the groups do not differ in the integrity of the corpus callosum (Fig. 3b). This suggests that ADT increases age-related white matter loss. We are continuing to examine other white matter regions as well as examine the relationship between white matter loss, fMRI signal in prefrontal cortex and memory.

Key Research Accomplishments:

(1) We developed diffusion tensor imaging and analysis methods to test the micromolecular structure and axon and myelin integrity in androgen deprived cancer patients.

(2) We developed high resolution functional magnetic resonance imaging with a cognitive activation paradigm to investigate memory dysfunction in patients on androgen deprivation.

(3) We tested each method and obtain preliminary data on brain changes that occur with prostate cancer and androgen deprivation treatment as compared to healthy men.

Reportable Outcomes:

1. This pilot study served as a training experience for a postdoctoral research fellow Dr. Mark Krause who has gone on to take a tenure-track position assistant professor position at Southern Oregon State University. It was also used to introduce a high school science teacher over two summers to functional brain imaging and prostate cancer as part of the Murdock Trust Partner's in Science program to improve science education in K-12.
2. This pilot study served to obtain data for a research proposal to the DOD on whether ADT increases the risk for neurodegenerative disease, and when in the course of ADT memory problems arise. This has been approved for funding and we are awaiting DOD approval of all IRB documents for the award allocation.
3. This pilot data will serve as preliminary data for a grant proposal to the NIH regarding ADT effects on emotion and decision-making in the next few months.

Manuscripts

Krause, M. & Janowsky, J.S. (in progress). Metamemory and functional neuroimaging of episodic memory encoding in older men. *(indirectly related to ADT study)*

Abstracts (These are in preparation as manuscripts)

Krause, M., Roalf, D.R., & Janowsky, J.S. Metamemory and functional neuroimaging of episodic memory encoding in older men. Association for Psychological Science, 2007.

Janowsky, J.S., Neiss, M., Young, L., Krause, M. Testosterone modifies cognition and brain activity in aging. International Society for Behavioral Neuroscience 2007.

Conclusion:

To our knowledge there have been no studies of the consequences on brain health of prostate cancer treatments in men despite data suggesting that ADT may cause memory or other cognitive impairments. Our study suggests that ADT increases the vulnerability for white matter loss in older men as well as memory loss. The white matter loss is selective to association or cognitive brain regions. These regions are those that are most vulnerable in aging, suggesting that ADT increases age-related white matter loss. The higher brain activity in prefrontal cortex in *both* groups of PC men is an unexpected result that will require additional analyses to understand it fully. These studies established techniques that can be used to assess neurotoxicity of prostate cancer treatments in the future, and provided information on neural vulnerabilities that may affect the quality of survivorship from PC. We are continuing to pursue these issues with a study of risk for dementia in men with

PC on ADT, and hope in the future to extend the DTI analyses as well as examine the response to the brain to emotional stimuli in men on ADT.

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Janowsky, J.S., Krause, M., Beer, T., The Brain Basis of Memory Loss with Androgen Deprivation Therapy: Methods Development and Preliminary Findings. IMPaCT Meeting, 9/2007, Atlanta, Georgia.

Appendices:

Tables and Figures

Table 1:
Subject Characteristics By Group

Group	N	Age M (SD)	Years Education M (SD)	MMSE M (SD)	GDS M (SD)	WAIS-R[a] M (SD)
Healthy	12	70.0 (6.6)	16.7 (2.3)	28.6 (1.2)	2.3 (2.2)	54.9 (6.2)
PC-ADT	11	69.6 (8.5)	16.2 (2.9)	28.6 (1.1)	3.3 (3.3)	54.8 (7.4)
PC-NonADT	12	69.0 (10.3)	15.5 (2.4)	28.6 (0.9)	3.6 (3.0)	54.5 (5.0)

Note. WAIS-R = Wechsler Adult Intelligence Scale-Revised vocabulary subtest, MMSE = Mini Mental State Exam, GDS = Geriatric Depression Scale.
[a]Expressed as WAIS-R vocabulary subtest raw scores.

Figure 1:

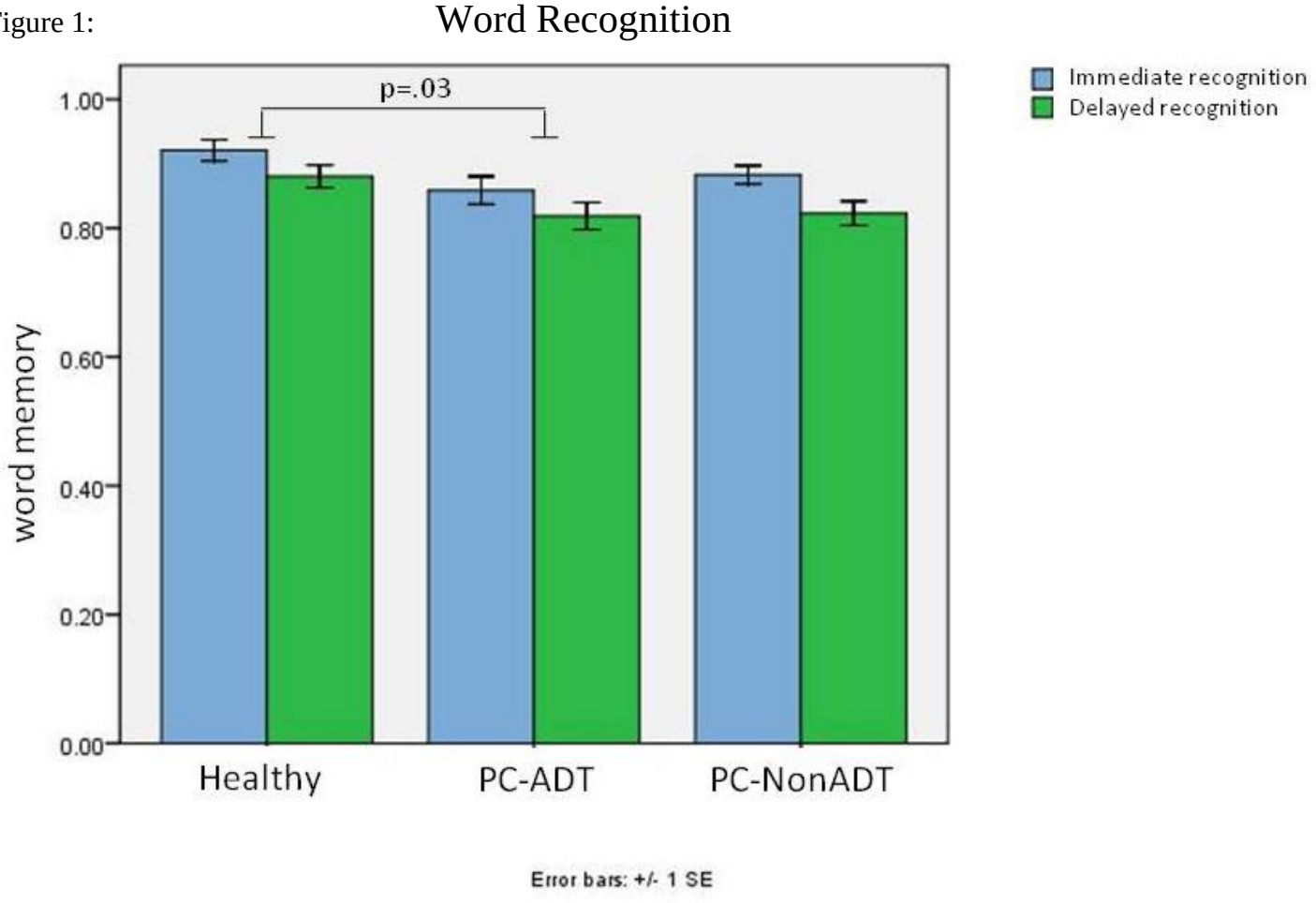

Figure 2a: Healthy

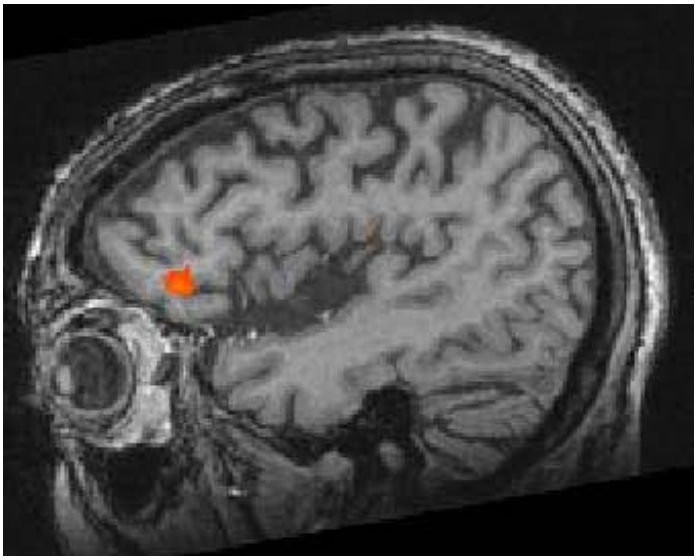

Figure 2b: PC-ADT

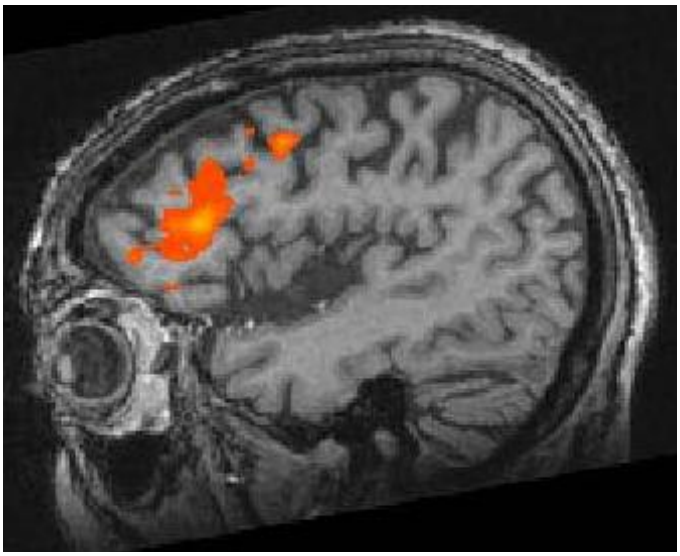

Figure 2c: PC-NonADT

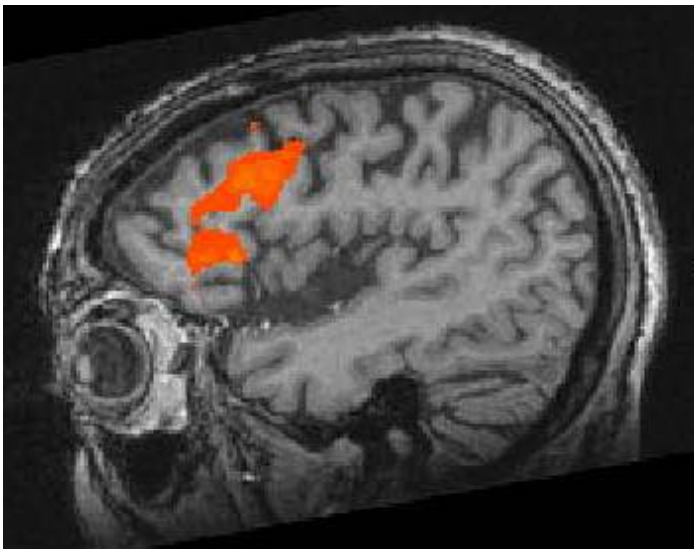

Figure 3a:

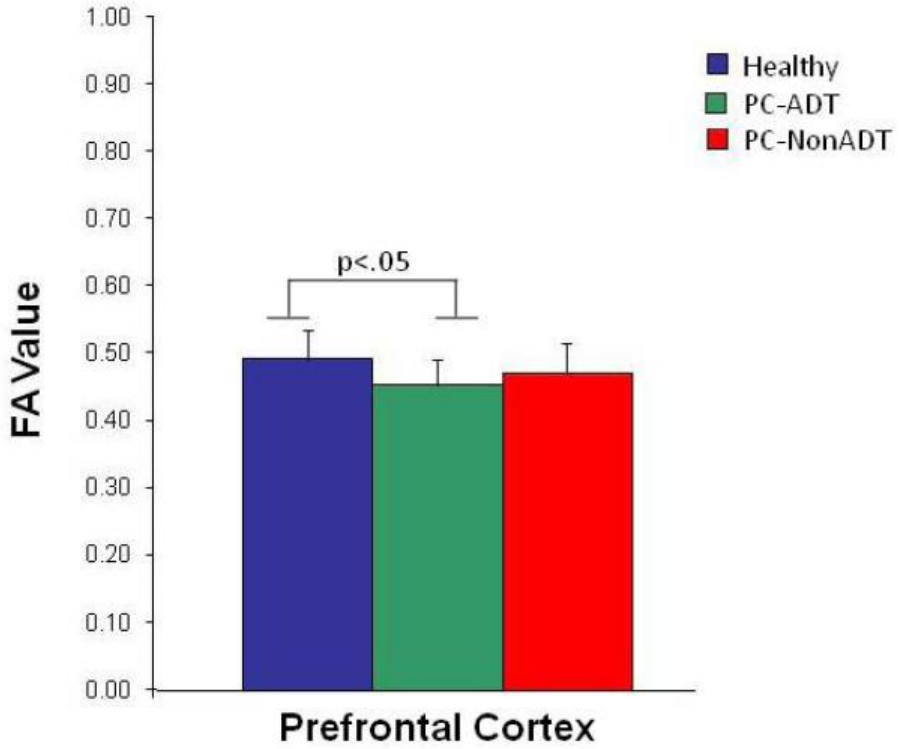

Figure 3b: